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REVIEW

The Effect of Biological Therapies on Psoriasis and Its Associated Comorbidities – New Facts and Future Options

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Abstract: Psoriasis is a chronic and complex disease that consists of characteristic cutaneous lesions and is frequently accompanied by systemic comorbidities caused by the chronic inflammatory state. The most common such comorbidities are hypertension, diabetes mellitus, dyslipidemia, inflammatory bowel diseases, depression, anxiety, neoplasia, and non-alcoholic fatty liver disease. Therefore, it is of utmost importance to simultaneously treat both psoriasis and the associated conditions with the best therapies available to improve patients' life quality. Therefore, this review aims to evaluate the effects of biological therapies on both psoriasis and its comorbidities and also to highlight other future options.

Keywords: psoriasis, chronic inflammation, biological therapies

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory disease that affects approximately 125 million people, or around 2% of the world population [1-3]. It has a bimodal incidence, with peaks between 16-20 years and between 57-60 years, with almost 70% of the cases before the age of 40 years [4]. On the other hand, due to an increase in life expectancy, the number of patients with psoriasis who are over 65 years is increasing, and that represents a therapeutic challenge, as the treatment has to be modulated in order to prevent drug interactions and not interfere with other comorbidities [4].

Psoriasis is mainly characterized by specific cutaneous lesions, but also by systemic involvement, the most frequent associated comorbidities being hypertension, diabetes mellitus, dyslipidemia, depression, anxiety, neoplasia, and non-alcoholic fatty liver disease [1,5]. The most common form of psoriasis is psoriasis vulgaris, which consists of well-defined erythematous plaques covered with silvery scales, most often found on knees, elbows, and scalp [6,7]. Other possible forms are guttate psoriasis, which affects most frequently children and young people, usually after streptococcal infections, and consists of small, teardrop lesions on trunk and extremities, pustular psoriasis, a rare form, which is characterized by sterile pustules, and inverse psoriasis, which affects flexion surfaces [7,8]. In severe cases, psoriasis can evolve toward an erythrodermic form affecting over 90% of the body surface, a condition that requires urgent medical intervention [9]. The pathophysiologic mechanisms are represented by an abnormal activation of the immune system, especially of T helper lymphocytes – Th1 and Th17, the next step being the production of proinflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukin 17 and 23 [10]. The result is the proliferation of keratinocytes and local inflammation, with the formation of the characteristic psoriasis plaques [10].

The diagnosis is mainly clinical, but there are also a few methods that can help in confirming the diagnosis, like reflectance confocal microscopy, which can show an increase in the size and number of dermal papillae, along with a dilation of capillary vessels, and dermoscopy [11,12].

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In this review, we aim to evaluate the psoriasis-associated comorbidities and to identify the best therapeutic approach in order to treat the patient as a whole.

PSORIASIS-ASSOCIATED COMORBIDITIES

The main link between psoriasis and all the comorbidities involved is the systemic inflammation, mediated by pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), and interleukin (IL) 17 and IL-23 [2]. This inflammation process involves mainly the vessels, aggravating atherosclerosis and making the cardiovascular diseases the most important comorbidities in patients with psoriasis, leading to a decrease in life expectancy of approximately 4-5 years [13-15]. Also, the risk of cardiovascular diseases is increased by over twofold in patients with psoriasis, independently of other risk factors, especially in severe forms and in patients under the age of 50 years, the mechanism involved being vascular inflammation that affects mainly coronary arteries and promotes early atherosclerosis [3,13,16]. Another very important aspect is that dyslipidemia, characterized by high levels of triglycerides and low-density lipoprotein cholesterol (LDL) and low levels of high-density lipoprotein cholesterol (HDL), has an essential role in the relationship between psoriasis and cardiovascular diseases [17]. Therefore, a correct management of the lipid levels is very important in order to lower the cardiovascular risk [17].

Obesity is another important comorbidity with a greater prevalence in patients with psoriasis, the severity of the last one being proportional to the body mass index [18]. The relationship between obesity and psoriasis is bidirectional. Psoriasis, due to chronic inflammation, leads to insulin resistance, promotes visceral fat deposition, and, in severe forms, limits mobilization, all of which increase the risk of becoming overweight. On the other hand, obesity is associated with a great number of pro-inflammatory adipokines, like leptin, and a low number of anti-inflammatory ones, an imbalance that aggravates local and systemic inflammation and also increases the risk of psoriasis by over one and a half times [18-21]. Another fact worth mentioning is that obesity can reduce the treatment efficiency due to a larger distribution volume and, therefore, indirectly aggravate the severity of psoriasis [19]. Moreover, almost 50% of the patients with psoriasis have metabolic syndrome, defined as the presence of at least three of the following: abdominal obesity (waist at least 102 cm in men and at least 88 cm in women), insulin resistance or increased level of blood glucose (at least 100 mg/dL), dyslipidemia (tryglicerides at least 150 mg/dL and/or HDL under 40 mg/dL in men and under 50 mg/dL in women), arterial hypertension (over 130/85 mmHg) [22]. The presence of metabolic syndrome is very important, as it is linked with a greater prevalence of cardiovascular diseases, fact that creates a vicious circle [20]. In addition, osteoporosis is more frequently encountered in patients with psoriasis due to the activation of the osteoclasts by the pro-inflammatory cytokines, and it also aggravates the prognosis [23].

Diabetes mellitus is one of the most frequent diseases worldwide and also a common comorbidity associated with psoriasis, both by chance and by similar pathophysiological mechanisms, the first link between these two diseases being noted as early as 1897 [14,24]. As it was already mentioned, psoriasis is characterized by systemic inflammation that can lead to insulin resistance and promote visceral fat deposition, mechanisms that can increase the risk for developing diabetes by up to two times compared with the general population [22]. Moreover, diabetes may be induced in certain patients with psoriasis by the use of corticosteroids in an attempt to control the severity of the disease, especially if other therapies are lacking [23].

Regarding mental ailments, patients with psoriasis have a greater risk than the general population, especially for depression, anxiety, and suicide [2]. The explanation is that the presence of cutaneous lesions leads to shame, low self-esteem, and isolation from other people, all of which result in a reduction of the quality of life [2]. In addition, a low level of melatonin is very frequent in this category of patients and may contribute to depression by inducing changes in the sleep pattern [25].

Table 1: Common hepatic adverse reactions of classical psoriasis treatment

Treatment	Effects on the liver	Sources
Methotrexate	• significant toxicity • can induce hepatic fibrosis and cirrhosis if used long time, especially in NAFLD	[32,33]
Cyclosporine A	• can increase lipid levels and favor hepatic steatosis • treatment should be carefully monitored in NAFLD	[34]
Acitretin	• can aggravate dyslipidemia and NAFLD in patients with metabolic syndrome	[35]
Dimethyl fumarate	• has a better safety profile and can reduce hepatic inflammation and oxidative stress • however, the liver function should be monitored carefully	[36]

NAFLD – non-alcoholic fatty liver disease

Last, but not least, one of the most common comorbidities recently associated with psoriasis is non-alcoholic fatty liver disease (NAFLD) [26]. It consists of excessive deposition of lipids in the liver that is not caused by alcohol consumption and that can progress to non-alcoholic steatohepatitis (NASH) and cirrhosis [27]. Epidemiological studies indicate that the prevalence of NAFLD is three times higher in this category of patients and also that the severity of psoriasis is proportional to that of NAFLD [28-30]. Moreover, an interesting study has revealed that almost 47% of the patients with psoriasis had NAFLD, and 22% even had biopsy-confirmed NASH

[29]. The diagnosis of NAFLD is established through imagistic methods like abdominal echography and elastography and laboratory tests for liver function, and fully confirmed by liver biopsy [31]. It is worth mentioning that NAFLD has a significant impact not only on the liver but also on other systems, including the heart, kidneys, and thyroid gland, which have to be carefully evaluated [29]. Thus, the combination of psoriasis and NAFLD leads to a greater cardiovascular risk and mortality, emphasizing once again the importance of treating the patient as a whole [28]. However, some of the therapies available for psoriasis can have a direct impact on the liver and be dangerous, especially if patients already have NAFLD [31]. Table I highlights the most common adverse hepatic reactions.

The dermatologist has an essential role in the early identification of psoriasis-associated comorbidities. The general management consists of carefully evaluation of the liver function and of cardiovascular risk using physical examination – body mass index calculation, arterial pressure, signs of dyslipidemia like the presence of xanthomas, imagistic methods – abdominal echography, liver elastography, coronarography in selected cases and laboratory tests, a wise choice of medication, especially in the presence of NAFLD, where biological therapies are the first recommended, and inclusion of non-pharmacological treatment options like a healthy diet with anti-inflammatory products and physical activity [13,17,18,27].

However, an integrated approach is mandatory for a correct and complete treatment, the most commonly involved medical fields being cardiology, gastroenterology, and psychology [37].

TREATMENT OF PSORIASIS AND ITS ASSOCIATED COMORBIDITIES

The treatment of psoriasis has significantly evolved in the last century, from empirical therapies to modern biological medications based on a more profound understanding of the pathophysiological mechanisms [19]. Initially, between 1920 and 1950, the treatment of psoriasis was focused on the clinical aspect, and the most common medications included arsenic, coal tar, salicylic acid, and dithranol [19]. In the 1950s, significant progress had been made by the development of topical corticosteroids, a very efficient form of medication, that rapidly became the gold standard of the treatment due to anti-inflammatory properties, but which lacked specific targets [38]. Moreover, if used extensively, adverse reactions occurred in the form of skin atrophy or tachyphylaxis [39]. A more important step toward better control of psoriasis was made when methotrexate and cyclosporine were discovered, both of them used in severe forms of psoriasis, but are also limited by the risk of significant hepatic and kidney adverse reactions or toxicity [32].

Table 2: Treatment of psoriasis: benefits on comorbidities, risks, and side effects

Medication	Benefits on comorbidities	Risks	Side effects	Sources
Methothrexate	↓systemic inflammation ↓cardiovascular risk	can aggravate NAFLD	hepatotoxicity	[32,33]
Cyclosporine	rapid control of severe psoriasis ↓ inflammation	arterial hypertension dyslipidemia	nephrotoxicity	[34]
TNF-α inhibitors (Infliximab, Adalimumab, Etanercept, Certolizumab)	↓ inflammation ↓cardiovascular risk ↓ risk of hepatic fibrosis ↓ insulin resistance first line in psoriatic arthritis	↓ efficiency in overweight patients modest weight gain	infections, especially TB autoimmune diseases: SLE or arthritis hepatotoxicity congestive HF rare: lymphoma and skin cancer	[49]
IL-17 inhibitors (Secukinumab, Ixekizumab, Brodalumab)	↓ inflammation improve dyslipidemia of choice in overweight patients	may ↑ IBD	fungal infections, especially local/systemic candidosis and respiratory infections pain, erythema, edema at the site of the injection rare: autoimmune diseases – SLE-like, anterior uveitis	[44,50]
IL-23 inhibitors (Guselkumab, Risankizumab, Tildrakizumab)	↓ inflammation ↓ insulin resistance improve hepatic function very good in the long term, with no negative impact on comorbidities	none	respiratory tract infections, especially viral pain, erythema, and edema at the site of the injection rare – autoimmune diseases – less frequent than with TNF-α or IL-17 inhibitors	[50]
Dual IL-12/23 inhibitors (Ustekinumab)	↓ vascular inflammation improve endothelial dysfunction	none		[51,52]
Small molecules (Apremilast)	↓ systemic inflammation improve glycemic metabolism modest weight loss, which can be of benefit	diarrhea		[53,54]

HF – heart failure; IBD – inflammatory bowel disease; IL – interleukin; NAFLD – non-alcoholic fatty liver disease; SLE – systemic lupus erythematosus; TB – tuberculosis; TNF-α – tumor necrosis factor alpha; ↓ - lower; ↑ - increase/aggravate

The true revolution of psoriasis treatment, especially of the severe forms, was provided by biological medication, which targeted specific inflammatory cytokines and modulated the pathophysiological mechanisms involved [40]. However, significant side effects are also common, therefore, a good collaboration with other subspecialities is mandatory [40]. The main representatives of this therapeutic class are: TNF-α inhibitors, IL-17 inhibitors, IL-23 inhibitors, and dual IL-12/23 inhibitors [41,42]. Of particular importance regarding comorbidities are the effects of these therapies on atherosclerosis, as a main cardiovascular risk factor. It is evaluated using the thickness of the intima and media of the vessels as measured by echography, the pulse-wave velocity, the aspect of the atherosclerotic plaques by CT angiography, and the level of C-reactive protein [43]. For example, it was revealed that IL-17 inhibitors like secukinumab significantly reduce the thickness of the intima and media of the vessels and also the arterial rigidity, much more than classical treatments like methotrexate and cyclosporine [44]. On the other hand, they seem to not affect the vascular inflammation evaluated by PET/CT or on metabolic markers like insulin or adiponectin [43]. Further studies are necessary to better explore these effects, especially in the long term, in order to simultaneously reduce both the severity of psoriasis and of cardiovascular risk, eventually by using therapies that target multiple cytokines at the same time [45].

As was mentioned before, another very frequent psoriasis-associated comorbidity is obesity, with almost 50% of the patients with psoriasis having metabolic syndrome [18,21,22]. Hence, a wise choice of medication is mandatory, especially because not all the therapeutic classes are effective in this context [13,37,46,47]. For example, TNF-α inhibitors have low efficiency in overweight patients and can even lead to an increase in weight [37,46,47]. IL-17 inhibitors, IL-23 inhibitors, and also small molecules (Apremilast) are of choice in this situation, due to their improvement in dyslipidemia, insulin resistance, and weight loss [47].

Last, but not least, NAFLD is a very important comorbidity that has to be taken into consideration when choosing a therapeutic approach, especially in patients with severe psoriasis, in whom this comorbidity also has a high prevalence [28,29]. Methotrexate or cyclosporine should be avoided if NAFLD is suspected, because they can aggravate it [28,47]. In this context, a much better solution nowadays is represented by the use of biological therapies, especially of TNF-α inhibitors, which can decrease the risk of hepatic fibrosis and decrease inflammation and dyslipidemia [1,48].

For an easier understanding, the most common therapies used in psoriasis are presented in Table 2, along with their benefits on psoriasis-associated comorbidities, risks involved, and the most important side effects.

NON-PHARMACOLOGICAL MANAGEMENT OF PSORIASIS AND ITS ASSOCIATED COMORBIDITIES

As was mentioned before, in this category of patients, it is of utmost importance to adopt an integrative approach, from modification of the lifestyle to a careful selection of the best medications in order to have as many benefits as possible with the minimum of side effects. Interventions on the lifestyle are mainly represented by aerobic exercises for at least 150 minutes per week, which reduce the risk of obesity and also improve the lean mass and the glucidic metabolism, management of the stress and of anxiety, and by adopting a healthy diet [46,55]. This last aspect is very important, as the Mediterranean diet is well documented to reduce inflammation and to prevent metabolic comorbidities [46]. It consists of healthy fats like olive oil, good quality proteins from fish, chicken, or eggs, fibers, vitamins, and minerals from fresh fruits and vegetables, and also of cereals and fermented dairy products [56]. In psoriasis, the Mediterranean diet has many important benefits: it reduces systemic inflammation, insulin resistance, and dyslipidemia and, consequently, reduces the risk of atherosclerosis, obesity, and NAFLD [46,55]. Regarding alcohol consumption, in modest quantities, the red wine has antioxidative properties due to resveratrol, but the frequent use has to be discouraged because it has a negative impact both on the severity of the disease, increasing the levels of pro-inflammatory cytokines like TNF-α and IL-17 that can aggravate the skin lesions and NAFLD, and on the treatment adherence and efficiency [46,57].

Table 3: Plants most commonly used in psoriasis

Plant	Effects	Sources
Aloe vera (Aloe barbadensis miller)	↓ local inflammation ↑ skin hydration prevents exfoliation	[58,64]
Turmeric (Curcuma longa)	– TNF-α – IL-6 ↓ local inflammation	[58,59]
Fish oil (Omega-3)	↓ systemic inflammation ↑ skin hydration ↑ PASI score	[56,58]
Chamomile (Matricaria chamomilla)	soothing skin effects ↓ local inflammation ↓ pruritus	[58,60]
Capsicum (Capsicum annuum)	↓ pain and pruritus ↓ local inflammation sometimes can irritate the skin	[58,65]
Fenugreek (Trigonella foenum-graecum)	↓ local inflammation ↑ skin barrier	[58,66]

IL – interleukin; TNF-α – tumor necrosis factor alpha; ↓ - decrease; ↑ - increase; – - inhibits

Medicinal plants are used in psoriasis as associated therapies due to their anti-inflammatory, antioxidative, and immune modulation properties. Even though the efficiency of these therapies is not well studied, some plants significantly reduced the symptoms of the disease when taken orally or applied topically [58]. Some of these plants are Aloe vera (Aloe barbadensis miller), Curcuma longa, omega-3 rich fish oil, Matricaria chamomilla, Capsicum annuum, and Trigonella foenum-graecum [58]. Aloe vera hydrates the skin and reduces local inflammation, while curcumin inhibits pro-inflammatory cytokines like TNF-α și IL-6 [58,59]. Omega-3 fatty acids from fish oil modulate the immune response and can decrease the severity of cutaneous lesions [56,58]. In addition, chamomile has soothing effects and is frequently topically utilized [60]. Last, but not least, capsaicine, which is a chili pepper extract, has analgesic and anti-inflammatory properties, decreasing pruritus and redness when used topically, while fenugreek can also be used orally, with similar anti-inflammatory and anti-oxidative characteristics [61–63]. On the other hand, future studies are needed to better explore their properties, and, because of this, patients must visit a specialist before taking any of these plants to prevent side effects or drug interactions. These plants and their properties in treating psoriasis are presented in Table 3.

CONCLUSION

Psoriasis is a complex disease, with a multitude of comorbidities that significantly affect the quality of patients` lives. Thus, the concomitant treatment is essential in reducing the risks, and a careful selection of the medication is mandatory, as not to aggravate the pre-existing or newly appeared conditions. The most common psoriasis-associated conditions are cardiovascular diseases, especially due to systemic inflammation that promotes early atherosclerosis, obesity, metabolic syndrome, dyslipidemia, NAFLD, diabetes, mental ailments like anxiety and depression, neoplasia, and inflammatory bowel disease. The greatest mortality is caused by cardiovascular diseases, the prevalence of them being over two times higher in patients with psoriasis. Consequently, pro-active management is essential, using both pharmacological and non-pharmacological measures, ideally in a personalized manner.

The novel, modern therapeutic options, which include biologic therapies, are very promising. They reduce systemic inflammation by targeting specific cytokines involved in the pathogenesis of psoriasis, like TNF-α, IL-17, IL-23, and, therefore, can improve both the cosmetic appearance and other conditions, especially when concurrently used with non-pharmacological interventions. Of them, IL-17 inhibitors seem to be of real benefit in reducing atherosclerosis and ameliorating cardiovascular diseases, the most dangerous risk in psoriasis patients. Also, IL-23 inhibitors and the small molecules (Apremilast) are of choice in overweight patients, decreasing dyslipidemia, insulin resistance, and obesity. Moreover, TNF-α inhibitors reduce the risk of NAFLD.

It can be concluded that nowadays there are many therapeutic options for treating psoriasis, and novel therapies targeting specific pathophysiological mechanisms that can modulate both psoriasis and its associated conditions. However, further studies are necessary to better identify the long-term effects of these modern, biological therapies.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration for publication elsewhere. This research received no external funding.

Authors' contribution

Conceptualization AFG, RSC, DOC and CC; methodology AFG, RSC, DOC and CC; validation MP, RSC, DOC, and CC; formal analysis AFG and CC; investigation AFG and DLC; resources AFG and DLC; data curation DOC; writing—original draft preparation AFG; writing—review and editing DOC, and CC; supervision MP, DOC and CC; project administration AFG, and DLC. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted under the Declaration of Helsinki. The research was conducted under ethical guidelines and regulations, ensuring compliance with all necessary protocols.

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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